REMARKS

Upon entry of the present amendment, claims 1, 2, 6-19, 21, and 32-52 will be pending in the present application.

Claims 16-18 are amended and new claims 33-52 are added to clarify the subject matter Applicants regard as their invention. Support for new claims 33 and 34 is provided below, new claims 35-51, which depend upon new claims 33 and/or 34 correspond to pending claims 2, 6-19, 21, and 32. Specifically, claims 16-18 are amended to recite "complex" rather than "heat shock protein" for clarity. Support for this amendment to claims 16-18 is found in the specification as filed at page 31, line 17, to page 32, line 3.

Support for new claims 33 and 34 is found in the specification as filed at page 7, lines 10-13 and 21-26, at page 8, lines 5-10; at page 9, lines 17-27; and at page 9, line 34, to page 10, line 8; at page 10, lines 26-29; at page 11, line 33 to page 12, line 8.

Support for new claim 35 is found in the specification as filed at page 9, lines 34-36, and at page 11, lines 25-30. Support for new claim 36 is found in the specification as filed at page 11, lines 25-30. Support new claim 37 is found at page 11, lines 25-28.

Support for new claims 38 and 39 is found in the specification as filed at page 7, lines 21-26. Support for new claims 40 and 41 is found in the specification as filed at page 8, lines 9-10. Support for new claim 42 is found in the specification as filed at page 8, lines 7-9 and 35-28.

Support for new claim 43 is found in the specification as filed at page 10, lines 26-29. Support for new claims 44 and 45 is found in the specification as filed at page 36, lines 23-27, and at page 36, lines 10-12.

Support for new claims 46-48 is found in the specification as filed at page 31, line 17, to page 32, line 3. Support for new claim 49 is found in the specification as filed at page 37, lines 13-23, and at page 38, lines 1-4. Support for new claim 50 is found in the specification as filed at page 10, lines 4-8. Support new claim 51 is found in Section 5.2.1 and its subsections, pp. 13-20 and the Examples in Sections 6 and 7, which describe protocols which produce a population of complexes; and at page 9, lines 27-31, page 12, lines 28-30, and at page 26, lines 26-36, which indicate that a purified population of endogenous hsp-peptide complexes comprises a population of different peptides.

Support for new claim 52 is found at page 7, lines 21-26.

Accordingly, all the amendments to the claims are fully supported by the specification as filed. No new matter has been added.

INTERVIEW SUMMARY

Applicant, Assignee, and Applicants' representatives thank Examiner Gerald R. Ewoldt and Supervisory Patent Examiner (SPE) Christina Chan for the courtesy of the recent interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants submit the following statement of the substance of the telephonic interview held on September 17, 2003 between Examiners Gerald R. Ewoldt and Christina Chan and Applicant Pramod K. Srivastava, assignee representative Daniel L. Levey, and Applicants' representatives Adriane M. Antler and Michael J. Ryan, in connection with the above-identified application.

Attorney for Applicant Adriane M. Antler discussed each of the four references cited under 35 U.S.C. § 103 against the claims of the above-captioned application in the Office Action mailed March 21, 2003, and explained why the references did not support the interchangeability of heat shock proteins for the treatment and prevention of graft rejection, and why the claimed invention was nonobvious in view of the cited references. Dr. Antler also presented Applicants' position as to why claims 16-18 of the above-captioned application are not indefinite under 35 U.S.C. § 112.

With respect to the § 103 rejection, SPE Christina Chan suggested that it would be helpful for Applicants, in their response, to emphasize and provide references evidencing the dissimilarity between hsps of different families (as opposed to the similarity between hsps within a particular family).

SPE Chan stated that she and Examiner Ewoldt had some concerns regarding enablement of the breadth of claim 1, since it covered all hsps other than hsp60 or cpn10. In response, Dr. Antler pointed out that Applicants had presented evidence supporting the use of hsp90 family members, as exemplified by the gp96 data in the instant specification, and hsp70 family members, as exemplified by International Publication WO 02/072133 (which had been provided to Examiner Ewoldt), and that this evidence supported the allowance of claims specifying hsp70 and hsp90 family members and thus additionally broad claim 1.

Further details of the remarks presented in support of patentability are found in the sections below.

The Rejection Under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claims 16-18 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, because they do not recite an amount of the specified composition to be

administered (Office Action at pages 2-3). More specifically, the Examiner notes that, although "the composition might contain a specific amount of hsp, e.g., 100 μg, said 100 μg of hsp might be present in a gram of composition or a ton of composition."

In response, Applicants note that claim 1 recites "administration of a composition" while claims 16-18 (which depend on claim 1), as amended, recite the range for the amount of hsp-peptide complex present in that composition. Applicants therefore agree with the Examiner that that claims 16-18 do not recite an amount of composition to be administered. Rather, claims 16-18 specify (by way of a range) the amount of hsp-peptide complex present in the composition that is administered.

In this context, Applicants respectfully request that the Examiner direct his attention to the relevant legal standard which has been articulated as follows

> The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention Section 112 demands no more. *Miles Laboratories v. Shandon Inc.* 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993) (internal citations omitted).

In view of this standard, Applicants respectfully submit that recitation of "the amount of complex is in the range of 5 μg to 5000 μg," "100 μg or more," or "200 μg or more," in claims 16-18 is not indefinite because it teaches those of ordinary skill in the art the proper dose of hsp-peptide complex to be used in the claimed methods. Moreover, Applicants respectfully submit that those of ordinary skill in the art should be able readily to determine an appropriate amount of composition that will contain the specified amount of complex, since it is well within the routine skill of one skilled in the art to calculate weight from concentration and volume, and *vice versa*. Accordingly, Applicants respectfully submit that claims 16-18 meet the legal standard for definiteness, and therefore respectfully request that the rejection of claims 16-18 under 35 U.S.C. § 112, second paragraph, be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 1, 2, 6-19, 21, and 32, are rejected under 35 U.S.C. § 103(a) as allegedly obvious over WO 95/15338 (hereafter "the '338 publication") and U.S. Patent No. 5,993,803 ("the '803 patent"), in view of U.S. Patent No. 5,750,119 ("the '119 patent") and Cohen (1992), "Autoimmunity to hsp65 and the Immunologic Paradigm," in Advances in Internal Medicine, 37: 295-311 (Mosby - Year Book Inc.) ("Cohen") for the reasons provided at pages 3-5 of the Office Action, as well as for the reasons of record as provided in the Office Action mailed March 7, 2002 ("Paper No. 13").

The basis of this rejection under § 103 appears to be the Examiner's position that since heat shock proteins have one function in common, it necessarily follows that heat shock proteins are interchangeable with one another for all purposes. Accordingly, the Examiner alleges that the methods of treating and preventing graft rejection of the present invention are obvious over the teaching of the cited art. Applicants, respectfully, do not agree.

The '338 publication teaches that mammalian cpn10 has immunosuppressive activity, and that administration of mammalian cpn10 prolonged the survival of skin grafts in rats (*see e.g.*, Table 2 at page 38 and Example 3, at page 17, line 33, to page 19, line 6). The '338 publication also teaches that mammalian cpn10 and early pregnancy factor ("EPF") are the same protein (page 5, lines 13-20).

However, the '338 publication also teaches that mammalian cpn10 is not interchangeable with other heat shock proteins. For example, at page 10, lines 8-19, it was demonstrated that two other heat shock proteins, bacterial cpn60 ("GroEL") and bacterial cpn10 ("GroES"), were inactive in the rosette inhibition assay of immunosuppressive activity. The latter result is particularly important since GroES is a homolog of mammalian cpn10 (page 10, lines 14-15).

Therefore, the '338 publication not only does not teach the use of any heat shock protein other than mammalian cpn10 for the treatment or prevention of graft rejection, it also indicates that mammalian cpn10 is not interchangeable with other heat shock proteins for such purposes. Accordingly, Applicants respectfully submit that the teaching of the '338 publication is limited specifically to the use of mammalian cpn10 for preventing graft rejection.

The '803 patent discloses the reduction of host vs. graft rejection, based on down-regulating hsp60 autoimmunity. The '803 patent teaches that hsp60 is an autoantigen that is upregulated (overexpressed) in donor grafts (see col. 3, lines 37-39), and thus down-regulating autoimmunity can down-regulate foreign immunity (*i.e.*, graft rejection) (see col. 3, lines 50-52). However, hsp60 is the only hsp that is taught to have these particular attributes and thus work in such fashion to inhibit graft rejection. Moreover, the '803 patent contains evidence that this use in reducing graft rejection is not only hsp-specific, it is also epitope-specific. The '803 patent discloses that certain hsp60 peptides, but not other hsp60 peptides, inhibit the rejection of foreign skin (see Fig. 4, and col. 13, lines 19-33). Moreover, the '803 patent discloses that an immunogenic peptide of the closely-related *Mycobacterial* hsp60, also did not prolong survival of the allograft" (col. 13, lines 25-28).

The above discussion makes it clear that the teachings of the '338 publication and the '803 patent with respect to inhibiting graft rejection are limited to cpn10 and hsp60

respectively, for the reasons discussed above. The dissimilarities between hsps of different families also supports the limited nature of the teachings of these references, and evidences the lack of expected interchangeability among hsps of different families for such purposes.

In support of the foregoing, the Examiner's attention is directed to Lindquist *et al.* (1988) "The Heat-Shock Proteins," *Ann. Rev. Genet.* 22: 631-77 (Reference BJ), ("Lindquist"). Lindquist teaches that sequence analysis of members of the hsp90 family of proteins has revealed that these proteins are highly conserved, and the hsp90 proteins of "even the most distantly related eukaryotes have 50% amino-acid identity, and all have greater than 40% identity with the *Escherichia coli* [hsp90] protein." (Lindquist at 634, last paragraph). Members of the hsp70 family are also closely related to one another, with all the hsp70-encoding genes identified prior to 1988 exhibiting "greater than 50% identity over their entire length." (Lindquist at 641, first paragraph).

However, other than one particular four-amino acid sequence, members of the hsp70 family have "little or no homology" with members of the hsp90 family (Lindquist at 635, first paragraph).

Therefore, although there is substantial conservation of amino acid sequence among members within a hsp family, there is little to no significant sequence homology between members of different hsp families. This point is further supported by the results of a BLAST comparison of amino acid sequences of members of different hsp families, which is attached hereto as Exhibit 1. This Exhibit provides the results of amino acid sequence comparisons between the following representative members of different heat shock protein families: cpn10, GroES, cpn60, GroEL, hsp70, hsp90, and gp96. [1]

With respect to the '119 patent, this reference dose not rectify the deficiencies of the '338 publication and the '803 patent, since it does not teach the interchangeability of hsps in inhibiting graft rejection. The '119 patent does teach the interchangeability of hsps in the method of the invention of the '119 patent, which is very different from inhibiting graft rejection. In the '119 patent, hsps function to noncovalently complex to endogenous peptides in tumor cells; these complexes are then isolated from tumor cells and used to treat cancer by stimulating an immune response against the complexed tumor peptides. Clearly a very different function is presented in the '119 patent, that of stimulating an anti-tumor immune

[1] These sequence comparisons were carried out using pairwise protein BLAST comparisons (pblast), available at www.ncbi.nlm.nih.gov/BLAST which is described in Tatusova *et al.* (1999) "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences," *FEMS Microbiol. Lett.* 174: 247-250 (Ref. CN). Default parameters were used except the comparisons were done without use of the "Filter" option, which masks segments of the query sequence having low compositional complexity.

response, as opposed to treating or preventing graft rejection (which is accomplished presumably by inhibiting the underlying immune response). [2]

Cohen teaches that prokaryotic hsp65 (also known as hsp60) is the "common antigen" of bacteria while the closely-related human homolog, mammalian hsp65, may be an autoantigen involved in the induction of autoimmune diseases such as diabetes, and that hsp65 peptides can be used to treat insulin-dependent diabetes mellitus ("IDDM") (page 304, in the paragraph number 3). Cohen mentions that there is significant evolutionary conservation of amino acid sequence homology within an hsp subfamily (referred to as "family" hereinabove and in the specification):

> [m]olecules of hsp constitute a family of proteins divided into subfamilies named for their approximate molecular masses in kilodaltons: hsp90, hsp70, hsp65 (also termed hsp60), and other, lower-molecular-weight proteins. Members of each hsp subfamily are produced by widely different creatures. Nevertheless, they are characterized by high degrees of sequence homology (page 297, last paragraph).

However, Cohen does not suggest that there are comparable similarities between members of different hsp subfamilies, nor does Cohen teach anything in connection with methods or reagents for the treatment or prevention of graft rejection. Accordingly, Cohen does not go beyond the teachings of the '803 patent (note that the same I.R. Cohen is the author of Cohen and an inventor of the '803 patent). Thus, Cohen does not rectify the deficiencies of the other cited references in that it does not support the interchangeability of hsps from different families, particularly in view of the evidence to the contrary discussed above.

In summary, Applicants conclude that for the reasons provided above: (1) the teaching of the '803 patent is limited to the use of hsp60 and certain peptides thereof for minimizing the severity of graft rejection; (2) the teaching of the '338 publication is limited to the use of mammalian cpn10 for treatment and prevention of graft rejection; (3) neither Cohen nor the '119 patent (nor the '803 patent or '338 publication), either taken alone or in combination, teach that heat shock proteins are interchangeable with one another for purposes of treating or preventing graft rejection; (4) both the '803 patent and the '338 publication would suggest to one of ordinary skill in the art that another hsp, *e.g.* a member of either the hsp70 or hsp90 family, could not be substituted for the particular hsp disclosed, *i.e.*, hsp60

[2] Applicants also note that the '338 publication teaches that cpn10 stimulates tumor cell growth (p. 4, line 21-22; p. 5, lines 18-19).

and mammalian cpn10, respectively; and (5) the art teaches that hsps of different families are dissimilar in sequence.

Applicants therefore also submit that there is no basis in the art cited by the Examiner, absent hindsight analysis using Applicants' application as a blueprint, that would support substitution of hsp60 and/or mammalian cpn10 with another heat shock protein in either the method of the '803 patent or the '338 publication.

Therefore, Applicants respectfully submit that independent claim 1, and therefore claims 2, 6-19, 21 and 32 dependent thereon, [3] are not obvious over the combination of the '338 publication, the '803 patent, Cohen, and the '119 patent. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 6-19, and 21 as obvious under 35 U.S.C. § 103 over the '338 publication, the '803 patent, Cohen, and the '119 patent, be withdrawn.

Enablement of the Claimed Invention

Applicants submit that the claimed invention is fully enabled as shown by the evidence provided in the specification as filed supporting the use of hsp90 family members (as exemplified by the gp96 data in the instant specification), and the use of hsp70 family members, as exemplified by International Publication WO 02/072133 ("the '133 publication). The '133 publication, which is entitled IMMUNOMODULATORY PROPERTIES OF BIP, discloses that BiP, a member of the hsp70 family of heat shock proteins[4], may be used for treatment and prevention of graft rejection (*see e.g.* '133 publication, at page 5, lines 6-16). Accordingly, Applicants submit that this evidence enables claims specifying hsp70 and hsp90 family members and thus additionally broad claim 1.

---

[3] "Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." In re Fine 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)

[4] Gething *et al.* (1992) "Protein Folding in the Cell," Nature 355: 33-45; Table 1, at page 35. (Reference AW)

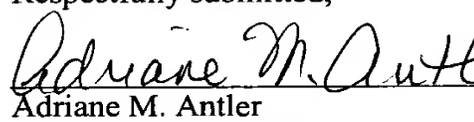
Conclusion

Applicants believe that each ground of rejection of the pending claims has been successfully overcome or obviated. Accordingly, Applicants respectfully request that the rejection of claims 16-18 under 35 U.S.C. § 112, second paragraph, and the rejection of claims 1, 2, 6-19, 21, and 32, under 35 U.S.C. § 103, be withdrawn.

Applicants submit that the entire application is now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: September 22, 2003



32,605 (Reg. No.)

Adriane M. Antler
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090